General

Guideline Title

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.

Bibliographic Source(s)

World Health Organization (WHO). Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva (Switzerland): World Health Organization (WHO); 2015 Mar. 134 p. [600 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The definitions for the strength of the recommendations (strong, conditional) and the quality of evidence (high, moderate, low, very low) are provided at the end of the "Major Recommendations" field.

Non-invasive Assessment of Liver Disease Stage at Baseline and during Follow up

Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g., FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint. (Conditional recommendation, low quality of evidence)

Who to Treat and Who Not to Treat in Persons with Chronic Hepatitis B

Who to Treat

As a priority, all adults, adolescents and children with chronic hepatitis B (CHB) and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of alanine aminotransferase (ALT) levels, hepatitis B e antigen (HBeAg) status or hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels. (Strong recommendation, moderate quality of evidence)

Treatment is recommended for adults with CHB who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20,000 IU/mL), regardless of HBeAg status. (Strong recommendation, moderate quality of evidence)

Where HBV DNA testing is not available: Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status. (Conditional recommendation, low quality of evidence)

Existing Recommendation for HBV/Human Immunodeficiency Virus (HIV)-Coinfected Persons[1]

In HBV/HIV-coinfected individuals, antiretroviral therapy (ART) should be initiated in all those with evidence of severe chronic liver disease, regardless of CD4 count; and in all those with a CD4 count ≤500 cells/mm^3, regardless of stage of liver disease. (Strong recommendation, low quality of evidence)

[1]Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013. These guidelines will be updated in 2015.

Who Not to Treat But Continue to Monitor

Antiviral therapy is not recommended and can be deferred in persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), and with persistently normal ALT levels low levels of HBV DNA replication (HBV DNA <2000 IU/mL), regardless of HBeAg status or age. (Strong recommendation, low quality of evidence)

Where HBV DNA testing is not available: Treatment can be deferred in HBeAg-positive persons aged 30 years or less and persistently normal ALT levels. (Conditional recommendation, low quality of evidence)

Continued monitoring is necessary in all persons with CHB, but in particular those who do not currently meet the above-recommended criteria for who to treat or not treat, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. These include:

- Persons without cirrhosis aged 30 years or less, with HBV DNA levels >20,000 IU/mL but persistently normal ALT levels
- HBeAg-negative persons without cirrhosis aged 30 years or less, with HBV DNA levels that fluctuate between 2000 and 20,000 IU/mL, or who have intermittently abnormal ALT levels

Where HBV DNA testing is not available: Persons without cirrhosis aged 30 years or less, with persistently normal ALT levels, regardless of HBeAg status

First-Line Antiviral Therapies for Chronic Hepatitis B

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. (Strong recommendation, moderate quality of evidence)

NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. (Strong recommendation, moderate quality of evidence)

Existing Recommendation for HBV/HIV-Coinfected Persons[1]

In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. (Strong recommendation, moderate quality of evidence)

[1]Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

Second-Line Antiviral Therapies for the Management of Treatment Failure

In persons with confirmed or suspected antiviral resistance (i.e., history of prior exposure or primary non-response) to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended. (Strong recommendation, low quality of evidence)

When to Stop Treatment

Lifelong NA Therapy

All persons with cirrhosis based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with NAs, and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. (Strong recommendation, low quality of evidence)

Discontinuation

Discontinuation of NA therapy may be considered exceptionally in:

- Persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults)
- And who can be followed carefully long term for reactivation
- And if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) and after completion of at least one additional year of treatment
- And in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (*where HBV DNA testing is available*)

Where HBV DNA testing is not available: Discontinuation of NA therapy may be considered in persons who have evidence of persistent hepatitis B surface antigen (HBsAg) loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status. (Conditional recommendation, low quality of evidence)

Retreatment

Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again) (*where HBV DNA testing is available*). (Strong recommendation, low quality of evidence)

Monitoring

Monitoring for Disease Progression and Treatment Response in Persons with CHB prior to, during and Post-treatment

It is recommended that the following be monitored at least annually:

- ALT level (and AST for APRI), HBsAg, HBeAg, and HBV DNA levels (where HBV DNA testing is available)
- Non-invasive tests (APRI score or FibroScan) to assess for the presence of cirrhosis, in those without cirrhosis at baseline
- If on treatment, adherence should be monitored regularly and at each visit. (Strong recommendation, moderate quality of evidence)

More Frequent Monitoring

In persons who do not yet meet the criteria for antiviral therapy: More frequent monitoring for disease progression may be indicated in: persons who have intermittently abnormal ALT levels or HBV DNA levels that fluctuate between 2000 IU/mL and 20,000 IU/mL (where HBV DNA testing is available), and in HIV-coinfected persons. (Conditional recommendation, low quality of evidence)

In persons on treatment or following treatment discontinuation: More frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons with more advanced disease (compensated or decompensated cirrhosis); during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV-coinfected persons; and in persons after discontinuation of treatment. (Conditional recommendation, very low quality of evidence)

Monitoring for Tenofovir and Entecavir Toxicity

Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initiation of antiviral therapy.

Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children. (Conditional recommendation, very low quality of evidence)

Monitoring for Hepatocellular Carcinoma

Routine surveillance for hepatocellular carcinoma (HCC) with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:

- Persons with cirrhosis, regardless of age or other risk factors (Strong recommendation, low quality of evidence)
- Persons with a family history of HCC (Strong recommendation, low quality of evidence)
- Persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ≤2), and with HBV DNA level >2000 IU/mL (*where HBV DNA testing is available*). (Conditional recommendation, low quality of evidence)

Prevention

Infant and Neonatal Hepatitis B Vaccination

Existing Recommendations in Infants and Neonates[1]

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses.

[1]WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20.

Prevention of Mother-to-Child HBV Transmission Using Antiviral Therapy

In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.

Existing Recommendations in HIV-Infected Pregnant and Breastfeeding Women[2]

In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for prevention of mother-to-child transmission (PMTCT) and then stopped. (Strong recommendation, low to moderate quality of evidence)

[2]Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High	Further research is very unlikely to change the Guideline Development Group's confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on the Guidelines Development Group's confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Strength of Recommendations

The strength of a recommendation reflects the extent to which the Guidelines Development Group was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The strength is influenced by the following factors: the quality of the evidence, the balance of benefits and harms, values and preferences, resource use and the feasibility of the intervention.

Strong recommendations: A strong recommendation is one for which the Guidelines Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.

Conditional recommendations: A conditional recommendation is one for which the Guidelines Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the Guidelines Development Group is not confident about these trade-offs. The implications of a conditional recommendation are that, although most people or settings would adopt the recommendation, many would not or would do so only under certain conditions. The reasons for making a conditional recommendation include the absence of high-quality evidence, imprecision in outcome estimates, uncertainty regarding how individuals value the outcomes, small benefits, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

Clinical Algorithm(s)

An algorithm titled "Algorithm of WHO recommendations on the management of persons with chronic hepatitis B infection" is provided in the original guideline document.

Scope

Disease/Condition(s)

Chronic hepatitis B (CHB) infection and its complications, including cirrhosis and hepatocellular carcinoma (HCC)

Other Disease/Condition(s) Addressed

Human immunodeficiency virus (HIV)

Guideline Category

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Obstetrics and Gynecology

Pharmacology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

- To provide guidelines on the on the prevention, care and treatment of persons with chronic hepatitis B virus (HBV) infection – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more

- To provide a framework for the development or strengthening of hepatitis B treatment programmes in low- and middle-income countries (LMICs) that is also of relevance to some high-income countries
- To complement existing World Health Organization (WHO) guidance on the primary prevention of hepatitis B through both hepatitis B vaccination and by improving blood and injection safety, as well as guidance among persons who inject drugs (PWID) and other vulnerable groups, including those living with human immunodeficiency virus (HIV) infection

Target Population

Children, young people and adults with chronic hepatitis B (CHB) virus (HBV) infection including pregnant women, persons co-infected with human immunodeficiency virus (HIV) or tuberculosis, persons who inject drugs (PWID), dialysis and renal transplant recipients, health-care workers, and indigenous peoples

Interventions and Practices Considered

1. Non-invasive assessment of liver disease stage at baseline and during follow-up
    - Aspartate aminotransferase (AST)-to-platelet ratio index (APRI)
    - Transient elastography (e.g., FibroScan) or FibroTest
2. Deciding on who to treat and who not to treat in persons with chronic hepatitis B (CHB) infection
3. Initiating antiretroviral therapy for patients coinfected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV)
4. Monitoring persons without clinical evidence of cirrhosis in whom treatment can be deferred
5. First-line antiviral therapies
    - Nucleos(t)ide analogues (NAs) with a high barrier to drug resistance (tenofovir or entecavir)
    - NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) (not recommended)
    - For HBV/HIV-coinfection: tenofovir + lamivudine (or emtricitabine) + efavirenz
6. Second-line therapy for management of treatment failure: switch to tenofovir
7. Deciding when to stop treatment
    - Lifelong NA therapy
    - Discontinuing treatment in exceptional situations
    - Retreatment after stopping therapy and relapse
8. Monitoring for disease progression and treatment response prior to, during and post-treatment
    - Alanine aminotransferase (ALT) level (and AST for APRI), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and HBV deoxyribonucleic acid (DNA) levels (where HBV DNA testing is available)
    - Non-invasive tests (APRI score or FibroScan) to assess for the presence of cirrhosis, in those without cirrhosis at baseline
    - Monitoring treatment adherence
9. Monitoring for tenofovir and entecavir toxicity (measurement of renal function)
10. Routine surveillance for hepatocellular carcinoma (HCC) with abdominal ultrasound and alpha-fetoprotein testing
11. Prevention
    - Infant and neonatal hepatitis B vaccination
    - Prevention of mother-to-child HBV transmission using antiviral therapy

Major Outcomes Considered

- Risk of progression
- Incidence of hepatocellular carcinoma (HCC)
- Incidence of hepatic decompensation
- Liver-related and all-cause mortality
- Rates of alanine aminotransferase (ALT) normalization
- Sustained undetectable hepatitis B virus (HBV) deoxyribonucleic acid (DNA) levels
- Hepatitis B e antigen (HBeAg) seroconversion and hepatitis B surface antigen (HBsAg) loss
- Reversion of fibrosis stage
- Duration of response/relapse rates
- Severe adverse effects

- Diagnostic accuracy and performance of non-invasive tests (NITs) of antiviral drugs and antiviral resistance
- Transmission of HBsAg and newborn and infant HBsAg- and HBeAg seropositivity
- Cost-effectiveness

Note: See Web Appendix 1 (Population, Intervention, Comparator, Outcome [PICO] questions) for specific outcomes considered for each of the guideline questions (see the "Availability of Companion Documents" field).

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and patient-important outcomes. Criteria for inclusion and exclusion of literature (e.g., study design, sample size, duration of follow up) for the reviews were based on the evidence needed and available to answer the research questions.

Generally, the following databases were searched: Medline (PubMed), EMBASE, Science Citation Index Expanded, Biosis, CENTRAL, LILACS, and CINAHL, National Guideline Clearinghouse (NGC), National Health Service (NHS) Evidence Search, and others.

The specific databases searched, the search strategies, and summaries of evidence for all guideline questions are reported in Web Appendix 2 (see the "Availability of Companion Documents" field).

Number of Source Documents

Please refer to Web Appendix 2 (see the "Availability of Companion Documents" field) for the number of source documents included in the systematic review for each of the guideline questions, including the number of documents initially retrieved in the literature search and the number of documents included after removal of duplicates, application of inclusion/exclusion criteria, and quality appraisal.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High	Further research is very unlikely to change the Guideline Development Group's confidence in the estimate of effect.
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Very low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The quality of the evidence was assessed and either rated down or rated up based on the following criteria: *rated down* based on (i) risk of bias (using the Cochrane Risk of Bias assessment tool), including publication bias; (ii) inconsistency or heterogeneity; (iii) indirectness (addressing a different population than the one under consideration); or (iv) imprecision. Conversely, the quality of the evidence was *rated up* if there was no reason to rate it down, and if it met any of the following three criteria: (i) large effect size; (ii) dose–response; or (iii) plausible residual confounders (i.e., when biases from a study might be reducing the estimated apparent intervention effect). Based on the rating of the available evidence, the quality of evidence was categorized as high, moderate, low or very low (see the "Rating Scheme for the Strength of the Evidence" field). Summaries of the quality of evidence to address each outcome were entered in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiler software (GRADEpro 3.6) (see Web Appendix 2 [see the "Availability of Companion Documents" field]).

See Web Appendix 2 for additional information on data extraction, quality assessment, and meta-analysis for each of the guideline questions.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

World Health Organization (WHO) Guideline Development Process

These WHO guidelines were developed following the recommendations for standard guidelines as described in the *WHO Handbook for Guideline Development, 2012* (see the "Availability of Companion Documents" field). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was followed for this process. A Guidelines Development Group was formed, ensuring representation from various stakeholder groups, including members of organizations that represent persons living with chronic hepatitis, advocacy groups, researchers, clinicians and programme managers. Geographical representation and gender balance were also considerations in selecting Group members. There was an initial scoping and planning process to formulate questions across the continuum of hepatitis B care and treatment most relevant to low- and middle-income countries (LMICs) and determine patient-important outcomes. These questions were structured in PICO format (population, intervention, comparison, outcomes) and patient-important outcomes were identified for each research question (see Web Appendix 1 for PICO questions [see the "Availability of Companion Documents" field]). These outcomes were refined and ranked based on their importance for the patient population.

Systematic reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and patient-important outcomes. Criteria for inclusion and exclusion of literature (e.g., study design, sample size, duration of follow up) for the reviews were based on the evidence needed and available to answer the research questions (see the "Description of Methods Used to Collect/Select the Evidence" field of this summary and Web Appendix 2 [see the "Availability of Companion Documents" field]).

At the June 2014 meeting of the Guidelines Development Group, for each of the PICO questions (see Web Appendix 1), the results of the systematic reviews and the evidence profiles (see Web Appendix 2) were presented, and reviewed to ensure that there was understanding and agreement on the scoring criteria. Drug availability and costs of diagnostics and drugs were also considered based on the available evidence and presentations from invited external expert speakers. Recommendations were then formulated based on the overall quality of the evidence, in addition to other considerations, including the balance between benefits and harms, values and preferences, and resource implications (see Table 2.2 in the original guideline document). However, no formal survey of acceptability of the proposed interventions among patients or health-care workers was undertaken for these guidelines. These were assessed through discussions among members of the Guidelines Development Group. The strength of the recommendations was rated as either strong (the panel was confident that the benefits of the intervention outweighed the risks) or conditional (the panel considered that the benefits of the intervention probably outweighed the risks) (see the "Rating Scheme for the Strength of the Recommendations" field). Recommendations were then formulated and the wording finalized by the entire Group. Implementation needs were subsequently evaluated, and areas and topics requiring further research identified.

The final recommendations were agreed on by consensus during a teleconference in July 2014. After all of the comments and questions from members of the Guidelines Development Group were addressed, a draft document was prepared and circulated to the members of the Guidelines Development Group.

Roles

The Guidelines Development Group helped formulate the PICO questions, reviewed the evidence profiles, formulated and agreed upon the wording of the recommendations, and reviewed all drafts of the guidelines document. The peer reviewers reviewed the draft guidelines document and provided comments and suggested editorial changes.

The guideline methodologist ensured that the GRADE framework was appropriately applied throughout the guidelines development process. This included a review of the PICO questions, ensuring the comprehensiveness and quality of the systematic reviews, and preparation of evidence profiles and decision-making tables. The methodologist also provided guidance to the Guidelines Development Group in formulating the wording and strength of the recommendations.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

The strength of a recommendation reflects the extent to which the Guidelines Development Group was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The strength is influenced by the following factors: the quality of the evidence, the balance of benefits and harms, values and preferences, resource use and the feasibility of the intervention.

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Cost Analysis

Costs and financial implications (resource use) were considered in determining the strength of recommendations. Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness will more likely result in a strong recommendation.

Refer to the "Resource use" and "Resource considerations" sections of the original guideline document for cost discussions for each of the guideline topics, which focus chiefly on resources available in low- and middle-income countries.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The final recommendations were agreed on by consensus during a teleconference in July 2014. After all of the comments and questions from members of the Guidelines Development Group were addressed, a draft document was prepared and circulated to the members of the Guidelines Development Group. Suggested changes were incorporated into a second draft, which was circulated again to the Guidelines Development Group, as well as to the World Health organization (WHO) Steering Group, and external peer reviewers. This document was further revised to address their comments, but modifications to the recommendations or to the scope were not considered.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- If hepatitis B virus (HBV) replication can be suppressed, the accompanying reduction in chronic liver inflammation reduces the risk of cirrhosis and hepatocellular carcinoma (HCC).
- The Guidelines Development Group recommended the use of non-invasive tests (NITs) to assist in the assessment of stage of liver disease and diagnosis of cirrhosis, to help prioritize those at greatest risk of morbidity and mortality for antiviral therapy. This avoids the use of liver biopsy, which is an expensive and invasive procedure associated with patient discomfort, carries a small risk of serious bleeding and requires specialist histological interpretation for accurate staging.
- There is evidence that antiviral therapy can halve disease progression (including hepatic decompensation, HCC or liver-related death), and may also lead to regression of fibrosis and cirrhosis over the long term. Therefore, targeting treatment to persons with cirrhosis would also be an effective use of resources. Nucleos(t)ide analogue (NA) therapy can be safely administered even to those with decompensated cirrhosis. In settings where liver transplantation is an option, suppression of HBV deoxyribonucleic acid (DNA) will also decrease the risk of recurrence of hepatitis B post-liver transplantation.
- The advantages of stopping NA therapy are a finite duration of treatment, with improved adherence and retention in care, reduced costs, and minimization of renal and bone toxicity.
- The side-effect profile, convenience (once-daily oral administration) and minimal requirement for toxicity monitoring of tenofovir and entecavir favour their widespread acceptability to individuals and health-care workers in most countries, particularly in low- and middle-income countries (LMICs).
- The Guidelines Development Group considered that the overall benefits of screening high-risk persons with chronic hepatitis B (CHB) outweighed the potential harms. Affected individuals develop HCC in mid-to-late adulthood, and deaths from HCC drain health-care resources and productive capacity in LMICs where HBV infection is prevalent. HCC is generally silent until symptomatic (typically when large, i.e., >10 cm in size), and the prognosis is extremely poor in persons with advanced-stage symptomatic tumours and underlying hepatic dysfunction. Additional benefits of integrating routine monitoring for HCC alongside routine monitoring for disease progression are that it provides a further opportunity to detect the development of cirrhosis and initiate antiviral therapy to prevent progression to HCC or liver failure.
- Hepatitis B vaccination is considered safe and effective, and prevents mother-to-child transmission in 80% to 95% of cases.

See the "Summary of the evidence" and the "Rationale for the recommendations" sections of the original guideline document as well as Web Appendix 2 (see the "Availability of Companion Documents" field) for details on the balance of benefits and harms of specific recommendations.

Potential Harms

- Potential harms from the use of non-invasive tests (NITs) include treatment decisions based on either false-positive or false-negative aspartate aminotransferase (AST)-to-platelet ratio index (APRI) test results. A false-positive test result may lead to a patient being treated unnecessarily or prematurely, which would expose them to the inconvenience of long-term treatment, potential drug resistance as well as a small risk of drug toxicities. Conversely, a false-negative result means that a person with cirrhosis would not be identified by NITs, and may therefore not receive prompt antiviral therapy, which might prevent progression to decompensation or decrease the risk of developing hepatocellular carcinoma (HCC).
- Although tenofovir is associated with a risk of nephrotoxicity, hypophosphatemia, bone mineral loss and osteopenia, the evidence review showed a low risk of these adverse effects (ranging from 0.3% to 2% for nephrotoxicity) with long-term tenofovir or entecavir, even among human immunodeficiency virus (HIV)-infected persons, but particularly in the absence of risk factors.
- The disadvantages of nucleos(t)ide analogues (NAs) are that they require lifelong therapy in the majority, which is associated with high cumulative costs and a risk of drug resistance. The disadvantages of NA discontinuation are the risk of reactivation of suppressed disease

with discontinuation of therapy, resulting in an unpredictable worsening of disease and possible development of fulminant hepatitis and acute-on-chronic liver failure, as well as the risk of developing resistance with "stop–start" therapy. Persons who discontinue therapy will also require careful long-term follow up for early detection of relapse.

- Primary non-response (defined as less than 1 log decrease in hepatitis B virus [HBV] deoxyribonucleic acid [DNA] level after 3 months of treatment, in settings where HBV DNA testing is available) is rare in persons initiating and adherent to entecavir or tenofovir treatment, but can occur in persons treated with lamivudine, adefovir or telbivudine. Sequential treatment of persons with lamivudine-resistant chronic hepatitis B (CHB) with adefovir or telbivudine or entecavir can lead to the selection of multidrug-resistant hepatitis B and should be avoided.
- Potential harms of screening include false-positive alpha-fetoprotein and ultrasound detection of small lesions other than tumours, such as regenerative nodules in cirrhotic livers, which may not develop into malignant HCC, resulting in unnecessary and costly interventions, as well as the inconvenience of attending for screening visits. There is also a trade-off in duration of intervals between screenings. If the intervals are too long, this may delay the detection of HCC, particularly in non-cirrhotic persons. In contrast, if HCC surveillance is more frequently performed, there will be an associated increase in cost per diagnosis.
- Several potential harms of antiviral use in pregnancy need to be more fully evaluated. These include the risk of development of HIV and HBV drug resistance if less potent drugs, such as lamivudine, telbivudine or adefovir, are used in mothers with a high HBV DNA viral load, especially if the duration of therapy is insufficient to reduce viraemia to low levels, and risks of toxicity to the baby, including through breastfeeding.

See the "Summary of the evidence" and the "Rationale for the recommendations" sections of the original guideline document as well as Web Appendix 2 (see the "Availability of Companion Documents" field) for details on the balance of benefits and harms of specific recommendations.

Contraindications

Contraindications

- Absolute and relative contraindications to interferon (IFN) include the presence of decompensated cirrhosis and hypersplenism, thyroid disease, autoimmune diseases, severe coronary artery disease, renal transplant disease, pregnancy, seizures and psychiatric illness, concomitant use of certain drugs, retinopathy, thrombocytopenia or leucopenia. IFN also cannot be used in infants less than 1 year of age.
- At baseline, consider either avoidance of tenofovir and use of entecavir instead, or dose reduction of tenofovir, if the estimated glomerular filtration rate (eGFR) is <50 mL/min, or in those with risk factors for renal dysfunction, including long-term diabetes, uncontrolled hypertension or severe osteopenia/osteoporosis. The use of tenofovir is not recommended in children aged 2–12 years, or in any child with renal impairment. Use of tenofovir should be avoided with concurrent/recent use of adefovir or other nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, foscarnet, ganciclovir, vancomycin, cidofovir) due to the increased risk of renal adverse reactions.
- Transient elastography (FibroScan) is not feasible in the presence of ascites and is contraindicated in pregnant women.

Qualifying Statements

Qualifying Statements

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
- The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.
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Implementation of the Guideline

Description of Implementation Strategy

Disseminating and Monitoring Implementation of the Guidelines

The guidelines will be launched in March 2015 at the annual meeting of the Asian Pacific Association for the Study of the Liver, which brings together approximately 5000 persons involved in hepatitis care. The guidelines will also be accessible on the World Health Organization (WHO) Web site with links to other related Web sites, and translated into the official United Nations (UN) languages. The Secretariat staff will work with the hepatitis points of contact in the WHO regional offices to ensure dissemination to WHO country offices and ministries of health, as well as key international, regional and national collaborating centres (e.g., civil society, foundations, donors), and national programmes. Additional tools will be developed to support country implementation.

Implementation of these guidelines will be assessed by the number of countries that incorporate them into their national treatment guidelines. This will be monitored through the biannual survey that forms the basis for the WHO Global policy report on the prevention and control of viral hepatitis. In the future, the impact of the guidelines would be measured by monitoring the number of persons treated for chronic hepatitis B (CHB). However, at present, there is no monitoring system that can collect this information at a national level.

Implementation Based on Local Context

Implementation of the recommendations in these guidelines should be informed by local context, including national hepatitis B virus (HBV) epidemiology, health systems and laboratory capacity, supply systems for drugs and other commodities, availability of financial resources, the organization and capacity of the health system and anticipated cost–effectiveness of the various interventions. Chapter 12 of the original guideline document addresses decision-making and planning for the development of hepatitis treatment programmes, and implementation considerations for the key recommendations relevant to country programme managers.

Implementation Tools

Clinical Algorithm

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

World Health Organization (WHO). Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva (Switzerland): World Health Organization (WHO); 2015 Mar. 134 p. [600 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Mar

Guideline Developer(s)

World Health Organization - International Agency

Source(s) of Funding

Funding for the development of these guidelines was provided by the United States Centers for Disease Control and Prevention.

Guideline Committee

Guidelines Development Group

World Health Organization (WHO) Steering Group

Composition of Group That Authored the Guideline

Guidelines Development Group Chairs: Olufunmilayo Lesi (University of Lagos/Lagos University Teaching Hospital, Nigeria) and Brian McMahon (Alaska Native Tribal Health Consortium Alaska, USA)

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The guidelines were drafted by Geoffrey Dusheiko (UCL Institute of Liver and Digestive Health, Royal Free Hospital, UK) and Philippa Easterbrook (Global Hepatitis Programme, WHO). Additional contributions were provided by Emmanouil Tsochatzis (Royal Free Sheila Sherlock Liver Centre and UCL Institute for Liver and Digestive Health, UCL and Royal Free Hospital, UK), Huma Qureshi (Pakistan Medical Research Council, Pakistan), and Karine Lacombe (Hôpital Saint-Antoine, Sorbonne-Universités, France). Drafts were reviewed and input provided by the members of the Guidelines Development Group, peer reviewers, and WHO Secretariat staff. Bandana Malhotra edited the document.

Financial Disclosures/Conflicts of Interest

Management of Conflicts of Interest

In accordance with World Health Organization (WHO) policy, all members of the Guidelines Development Group and peer reviewers were required to complete and submit a WHO Declaration of Interest form (including participation in consulting and advisory panels, research support and financial investment) and, where appropriate, also provide a summary of research interests and activities. The WHO Secretariat then reviewed and assessed the declarations submitted by each member and, at the June 2014 meeting of the Guidelines Development Group, presented a summary to the Guidelines Development Group (see Web Appendix 3 [see the "Availability of Companion Documents" field]). The WHO Secretariat considered significant and predominant funding from a single company whose drug was being considered for use in the treatment of hepatitis B virus (HBV) (e.g., tenofovir). The Secretariat found no case where there was exclusive membership of an advisory panel, receipt of consulting fees or financial support through research grants from one pharmaceutical company. One member had received a research grant from Gilead, but this was for a community-based screening project, and unrelated to treatment. The Secretariat therefore concluded that no member should be excluded from actively taking part in formulating the recommendations during the meeting. For the peer review group, the WHO Secretariat was satisfied that there had been a transparent declaration of financial interests, and no case necessitated exclusion from the review process.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the World Health Organization (WHO) Web site.

Availability of Companion Documents

The following are available:

- Guideline development for the prevention, care and treatment of persons with chronic hepatitis B. Web Appendix 1. PICO questions for the WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B. Geneva (Switzerland): World Health Organization (WHO); 2015. 5 p. Available from the World Health Organization (WHO) Web site.
- Guideline development for the prevention, care and treatment of persons with chronic hepatitis B. Web Appendix 2. Systematic review reports and evidence summaries. Geneva (Switzerland): World Health Organization (WHO); 2015. 932 p. Available from the WHO Web site.
- Guideline development for the prevention, care and treatment of persons with chronic hepatitis B. Web Appendix 3. Management of conflicts of interest. Geneva (Switzerland): World Health Organization (WHO); 2015. 5 p. Available from the WHO Web site.
- WHO handbook for guideline development. Geneva (Switzerland): World Health Organization (WHO); 2012. 56 p. Available from the WHO Web site.

A variety of resources on hepatitis are available from the WHO Web site .

Patient Resources

The following are available:

- Hepatitis B: how can I protect myself? Online Q&A. Available from the World Health Organization (WHO) Web site .
- What is hepatitis? Online Q&A. Available from the WHO Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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